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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,419	07/24/2000	MAX F. ROTHSCHILD	P03815US1	2593

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EXAMINER	
EINSMANN, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/380,419	ROTHSCHILD ET AL.	
	Examiner	Art Unit	
	Juliet C Einsmann	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2002 and 29 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,20-23 and 28-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 20-23, and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/29/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 25 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *CRF problem report* .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/27/02 (paper number 20) has been entered. Claims 1, 2, 4-6, 10, 20, 22, 23, 28, 29, 31, 32, and 33 have been amended. Claims 1-12, 20-23, and 28-33 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The amendments to the specification provided on pages 2 and 3 of the response were not entered because they are not in proper form. The amendments should be resubmitted using the format which provides replacement paragraphs for amendments to the specification as required by rule 1.121.

3. The formal drawings have been received and are approved by the examiner.

Priority

4. Priority is granted in this case to the instant filing date. Although the cited provisional applications contain disclosure of the polymorphism used in the instant methods, they do not provide adequate support for the instantly claimed screening methods.

Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s):

(A) The sequence identifiers used on page 7 do not match up with the sequence listing.

(B) The sequences recited in Fig. 7 must be identified with proper sequence identifiers.

(C) The nucleic acid sequences recited in figure 5 must be identified with proper sequence identifiers.

It is noted that applicant attempted to correct these problems in paper number 20. However, that portion of the amendment was not entered because it was not in proper form. Thus, in order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must correct these problems. If applicant chooses to submit a new CRF and paper copy, Applicant must submit a new CRF and paper copy of the Sequence Listing containing these sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

6. The new CRF submitted 3/27/02 was damaged (see enclosed CRF problem report, paper number 21). Thus, a replacement CRF is required if applicant still desires for that CRF to be the CRF of record.

Claim Rejections - 35 USC § 112

7. Claims 1-12, 20-23, and 28-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of identifying a pig which possesses a genotype indicative of the pig having less back fat than pigs with a different genotype, indicative of the pig having a lower daily gain than pigs with a different genotype, or of pigs having a lower feed intake than a pig with a different genotype, wherein said method comprises screening DNA of the pig for a G → A point mutation at position 678 of SEQ ID NO: 1 (of the sequence listing) and wherein the absence of the mutation is indicative of a pig having the recited traits, does not reasonably provide enablement for methods which screen other animals or methods which utilize other polymorphisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The prior art teaches one polymorphism in humans which is associated with obesity (Yeo *et al.* 1998. Nature Genetics, Vol. 20, p. 111-112). Methods for screening humans using this polymorphism are also enabled. In addition, claims 28 and 31 have been amended so that they encompass screening methods using any gene, any polymorphism and any animal. These claims are included in this rejection insofar as they would pertain to screening of the MC4R gene.

Each of the rejected claims are broadly drawn to include at least one of the following: methods for screening any animal or methods for screening which utilize a polymorphism not limited to the single disclosed polymorphism in this application (i.e. the G → A point mutation at position 678 of SEQ ID NO: 1).

The specification provides a single working example which demonstrates that pigs homozygous for an G at position 678 of SEQ ID NO: 1 have less backfat, lower daily gain, and lower feed intake than pigs homozygous for an A at position 678. The prior art is silent with respect to other possible polymorphisms in the MC4R gene or with respect to the association of this particular polymorphism with any metabolic trait in any other animal. Neither the specification nor the prior art provide evidence of any universal correlation between polymorphisms in MC4R and metabolic traits which would conclusively associate the polymorphism instantly disclosed with metabolic traits in any other animal.

The art is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. The amount of direction or guidance presented in the specification and the prior art of only one point mutation in the MC4R gene of one species of animal is minimal, given that just the redundancy of the genetic code would allow for several thousand different sequences when conserved or non-conserved mutations are considered, millions of different sequences for the pig MC4R gene may exist which may, or may not, have substantial functional differences or association with the traits of interest herein. There are no working examples of additional sequences other than those disclosed in either the specification or the prior art.

Furthermore, there is no evidence in the specification provided that the identified polymorphism is causative of the observed traits. This is a significant absence of evidence, since it is possible that the polymorphism is merely a marker for the causative genotype. In light of the fact that the causative genotype has not been identified, it is unpredictable as to whether or

not markers which are linked to the instantly disclosed polymorphism would be informative for the traits of interest herein (for example, as claimed in claims 29 and 30).

Although the level of skill in the art of nucleic acid analysis is high (the Ph.D. degree with laboratory experience), the quantity of experimentation that would be necessary to determine even one additional polymorphism in the pig MC4R gene is substantial since there is no predictability for which sequences exist which code for polymorphisms in pig MC4R genes. Applicants have not disclosed how one would go about detecting additional polymorphisms associated with the traits of interest herein. Because there is no reason to expect that any additional polymorphism is associated with the instantly discussed metabolic traits and because of the very large number of possible polymorphisms, screening for additional polymorphisms that would be indicators of these traits would require the rearing and subsequent slaughtering of many, many pigs in order to analyze their metabolic traits and in order to screen the MC4R gene for informative polymorphisms. There is no evidence, however, of any frequency of significant polymorphisms. Further, even if polymorphisms were detected, the polymorphism may not correlate to polymorphic traits. The instantly disclosed polymorphism may be coincident with and unrelated to a different, unlinked (on the chromosome) polymorphism such as another MC4R polymorphism or a polymorphism in an undetermined gene that actually determines the metabolic traits. The instantly disclosed polymorphism would not have any meaning or effect, but might appear to influence metabolic traits due to it's close proximity to some other gene.

Furthermore, the level of unpredictability and the level of experimentation required to expand the instantly disclosed methods to include animals of other species are also quite high. There is no teaching in the specification that the disclosed polymorphism even exists in animals

of other species. Since there is not evidence that the disclosed polymorphism is causative of the traits (as discussed above), it is highly unpredictable as to whether the polymorphism would mark the same traits in other animals. Further, in order to provide such evidence the skilled artisan would be required to undertake extensive studies of the metabolic traits of hundreds upon hundreds of different individual animals of each of many different species of animal. Such experimentation would be inventive in itself.

Due to the broad nature of the claims, the presence of only one working example, the extreme unpredictability of polymorphisms in the art, combined with the absence of teaching in the prior and the large quantity of experimentation necessary in the art support a conclusion that undue experimentation is required to make and use the invention as broadly claimed.

8. Claims 1-12, 20-23, 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the purpose of the method as set forth in the preamble is unclear. The preamble indicates that the method is for "identifying an animal which possesses a genotype associated with variation in one or more favorable metabolic traits." This is unclear, because any animal, at least any pig with a MC4R gene would have a genotype that is associated with variation in one or more of the listed traits. Claim 1 does not specify that animals possessing genotypes indicative of particular traits are identified, merely that animals possessing genotypes associated with variation are identified. Thus, the claim remains unclear. Claims which depend from claim 1 are indefinite for this reason as well.

Claims 2, 4, 5, and 6 are further indefinite over the recitation "at base 678 in a PCR sequence of the MC4R gene" because this language does not clearly identify where within the nucleotide sequence of the MC4R gene the polymorphism is being identified. That is, the position of a nucleotide within a PCR product is entirely dependent upon the primers used to amplify the product. These claims do not indicate which primers are to be used, and therefore, the designation "at base 678 in a PCR sequence of the MC4R gene is arbitrary and fails to clearly identify the scope of the claim.

Claim 4 is further indefinite because it is not clear what portion of the claims "associated with variation in fat content" modifies. That is, it is not clear if the claim is indicating that the guanine is associated with variation in fat content or that the PCR sequence is associated with variation in fat content or that the MC4R gene is associated with variation in fat content.

Claim 12 is indefinite because it is not clear if it is a product claim or a method claim since it depends from method claim 10 but begins "the amplified gene sequence." The claim has been treated as a method claim herein because it depends from method claim 10.

Claims 20-23 are indefinite for failing to recite a final process step which agrees back with the preamble. Claims 20-23 are drawn to a method of identifying an animal which possesses a **desired** genotype having a genetic marker associated with variation in one or more metabolic traits (emphasis added). The final process step of the claims recites "wherein the presence of a TaqI restriction site identifies the presence of a polymorphic site in the MC4R gene associated with variation in one or more of the metabolic traits in the animal..." but the claim does not make the connection between the desired genotype and the presence of the TaqI restriction site. That is, the method steps of the claim designate how to know if there is a polymorphic site

"associated with variation" present, but it does not instruct how to identify an animal with a desired genotype. Claim 20 does not set forth any specific desired genotypes or how these are identified.

Claim 22 is indefinite over the recitation of "at base 678 of the amplified product" because claim 21 recites two amplified products and it is not clear which amplified product the claim intends. Furthermore, the claim is indefinite over the recitation "when a restriction enzyme which cuts at the same recognition site as Taq I is used" because it is not clear when the restriction enzyme is used or what it is used to digest. That is, is the restriction enzyme the same one that is recited in line 8 of claim 21 (and thus is Taq I) or is being used at some other time?

Claims 29 and 30 are indefinite over the recitation "alternative DNA marker" because it is not clear what this marker is an alternative to.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 28 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Tuggle et al. (US 5614364).

Tuggle et al. teach a method for selecting animals possessing a desired pair of alleles associated with variation in one or more favorable metabolic traits, wherein the metabolic trait is lower fat content, than animals without said alleles comprising:

obtaining a nucleic acid sample from an animal (Col. 11, line 55);

identifying the alleles associated with a desired metabolic trait (Col. 12, lines 30-37), and selecting the animals which have desired alleles (Col. 11, lines 37-40).

Tuggle et al. also teach a method of identifying animals to determine the association between a pair of alleles and one or more metabolic traits of interest selected from fat content, growth rate, and feed consumption, the method comprising:

obtaining a sample of animals from a line or breed of interest (Col. 6, lines 13-15),

preparing genomic DNA from each animal in the sample (Col. 6, lines 13-15),

determining the alleles present (Col. 6, lines 15-25), and

calculating the association between the alleles and the trait (Col. 6, line 44-Col. 8, line 67).

Thus, the teachings of Tuggle et al. anticipate claims 28 and 31.

Response to Remarks

The objections to the specification for lack of compliance with the sequence rules remain because the amendment to the specification were not entered because they were not in the proper format. Furthermore, even if the amendments were entered, the application still would not be in compliance with the sequence rules. Applicant correctly pointed out that the brief description of Fig. 5 identifies a sequence with a sequence identifier. However, Figure 5 recites three different sequences, each of which should be identified with sequence identifiers. Correction is required.

Applicants argue that they have shown that polymorphism in the MC4R gene has been located and is associated with the metabolic traits of fat content, growth rate, and feed consumption in animals. However, as pointed out in the rejections of record, this correlation has only been shown for pigs, not for all animals. Thus, this statement is correct in that pigs are

animals, but it is not true to say that applicant has shown this correlation for all animals. Applicants point out that this particular polymorphism is within a highly conserved region among melanocortin receptors and that they have provided an alignment of the predicted amino acid sequences of the pig MC4R with the MC4R protein from other species, demonstrating that the aspartic acid found at position 298 of the seventh transmembrane domain is very highly conserved in the MC4R protein among species. The fact that the MC4R protien is conserved among species is not sufficient to establish that this polymorphism exists in other species because there is no correlation between this conservation of sequence and the conservation of polymorphism among species. That is, there is no reason to believe that this same polymorphism would exist in other species, and no evidence has been provided that would support this assertion. The appearance of polymorphism among different species is highly unpredictable, as discussed in the rejection, and that the protein is conserved among species is not evidence that polymorphic events are also conserved among species.

Applicant's suggest at the bottom of page 9 and on page 11 that the claims have been amended to include the specific polymorphism disclosed in the instant rejection, thus alleviating the examiner's concerns about the unpredictability with regard to the prescence and functionality of polymorphic sites in genomic DNA. However, this is not persuasive because it does not appear that the claims as amended are so limited. For example, claim 1 recites "assaying for the presence of a polymorphism in the MC4R gene," which encompasses assaying for the prescence of any polymorphism in the MC4R gene. Furthermore, dependend claims 2 and 4-6 which appear to be an attempt to limit the claims to the specific polymorphism disclosed in the instant

specification are not clear because they do not properly identify the PCR product in which the polymorphism is being identified (see 112 2nd paragraph rejections). Furthermore, it is noted that the examiner's comments with regard to unpredictability are focused on the fact that it is highly unpredictable as to whether or not any other polymorphisms exist in the porcine MC4R gene OR whether or not the instant polymorphism exists in other species of animals which have a MC4R gene. Although it may be routine experimentation to search for such polymorphisms, this does not subtract from the fact that they actually may not exist. The art is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. First, it is unpredictable whether any additional polymorphisms exist in the porcine MC4R gene, or whether the instantly disclosed polymorphism is present in the genomes of other animals. Genetic polymorphisms are the elements which render individuals unique, but many genes are highly conserved and do not yield polymorphisms between individuals of a single species. Some genes even lack polymorphisms between members of different species. The specification and prior art provide no guidance as to whether any other polymorphisms exist, or whether the instantly disclosed polymorphism is present in the genomes of other animals besides pigs. Second, after a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with favorable meat quality. Thus, the claimed method of screening animals, for enablement of the full scope, requires the use of unpredictable and potentially non-existent products. As noted in In re Vaeck, 20 USPQ2d 1438 (CA FC 1991) regarding enablement, "This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse

and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. See Fisher, 427 F.2d at 839, 166 USPQ at 24." In this case, the genus is itself undefined and undue experimentation is required to identify which polymorphisms, none of which are known other than the disclosed example, have the utility of being associated with metabolic traits in animals.

Applicants argue that they need not understand or disclose how the polymorphism works or how it causes these metabolic traits. However, this is not persuasive. The point here is that if applicant knew that a causative relationship exists between the presence of this polymorphism and the observed traits, then, it may be more reasonable to assume that a similar polymorphism or mutation would be causative of these traits in other species of animals. But in fact, applicant has not disclosed that there is a causative relationship in this case, and in fact it is entirely possible that the disclosed polymorphism is merely a marker of some other genetic feature that is associated with these traits. That such marker relationship would exist in other species is highly unpredictable.

Applicant asserts that the "Examiner has interpreted that experimentation needed in such a way that effectively renders it impossible to claim the claim not only for the instant invention, but for any biological invention (response, page 13)." Other inventions are not being examined herein, so the examiner will not comment on "the claim" for any biological invention, but only for the instantly claimed invention. In the instant case, the examiner has not rejected the claims because they do not provide every single example or species covered by the claim, the examiner

has rejected the claims because they have large breadth, only single example is provided, and the subject area is highly unpredictable, for all of the reasons discussed herein and in the rejections. This situation differs tremendously from In re Angstadt, wherein a large number (forty) examples were provided, only one of which did not work. In this case, the court determined that there was sufficient guidance in an unpredictable art. The court further stated, however, that "each case must be determined by its own facts." In this case, only one example of a single polymorphism that is an indicator of specific metabolic traits in a single species of animals has been provided in a highly unpredictable art. Thus, unlike in In re Angstadt, the examiner concludes that undue experimentation would be necessary to practice the claimed invention commensurate in scope with the claims. Thus, the rejection is maintained.

Applicant asserts in the remarks (p. 16) that claim 1 has been amended to show a method for identifying an animal with favorable metabolic traits regarding fat content, growth rate and feed consumption. However, it appears from the claim that the claim still is drawn to a method of identifying an animal which possesses a genotype associated with variation in these particular metabolic traits. Amendment of the claim to recited, for example, "A method for identifying an animal with an increased likelihood of having less back fat than pigs with a different genotype, having a lower daily gain than pigs with a different genotype, or of pigs having a lower feed intake than a pig with a different genotype," provided that the process steps of the claim accomplish this preamble, may help to overcome this rejection.

It is noted that claim 5 could be further clarified by amending the language of the claim to read "wherein a marker for animals with lower feed intake than animals without the marker" would also help to clarify claim 5. Similar language would clarify claim 6.

Applicant asserts that claim 20 has been amended to recite a final process step that meets the preamble, however the examiner does not agree, for the reasons stated in the modified rejection based on the new claim language. Furthermore, applicant points the examiner to claim 22 to show the desired genotypes, however this is not persuasive for two reasons. First, this does not clarify claim 20. Second, the language of claim 22 does not clearly discuss or clarify that the genotypes being identified in that claim are the "desired" genotypes, it merely instructs as to how to identify "the site." Further clarification of these claims is required.

New 112 2nd rejections were made to address the amendments to the claims.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Einsmann
Examiner
Art Unit 1655

August 8, 2002